



THE FACTS ABOUT PENICILLIN ALLERGY: A REVIEW

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Abstract

Hypersensitivity reactions are the major problem in the use of penicillins. True penicillin allergy is rare with the estimated frequency of anaphylaxis at 1-5 per 10 000 cases of penicillin therapy. Hypersensitivity is however, its most important adverse reaction resulting in nausea, vomiting, pruritus, urticaria, wheezing, laryngeal oedema and ultimately, cardiovascular collapse. Identification of patients who erroneously carry β -lactam allergy leads to improved utilization of antibiotics and slows the spread of multiple drug-resistant bacteria. Cross-reactivity between penicillin and second and third generation cephalosporin is low and may be lower than the cross-reactivity between penicillin and unrelated antibiotics.

Key words: Penicillin, hypersensitivity, anaphylaxis, IgE, cross-sensitivity.

Introduction

Penicillin belongs to an important group of antibiotics called beta (β)-lactam antibiotics which are generally effective at eradicating common bacterial infections and are relatively inexpensive and therefore widely used to treat skin, ear, sinus and upper respiratory tract infections. This class of antibiotics includes penicillin and penicillin derivatives such as ampicillin and

amoxicillin as well as cephalosporins, monobactams, carbapenems and β -lactamase inhibitors. As with most drugs, penicillin exhibits common side effects and adverse reactions (Table 1). However, true drug allergy, which is IgE-mediated, accounts for very few of all reported adverse drug reactions [1, 2].

All forms of natural and semisynthetic penicillins can cause allergy, but it is more commonly seen after parenteral

than oral administration. Penicillin G is the most common drug implicated in drug allergy. Incidence is probably highest with procaine penicillin, as procaine itself is allergenic. The course of penicillin hypersensitivity is unpredictable i.e. an individual who tolerated penicillin earlier may show allergy on subsequent administration and *vice versa* [1].

Table 1: Adverse drug reactions associated with the use of penicillin.

Common adverse drug reactions.	Diarrhoea, nausea, rash, neurotoxicity, urticaria and/or super infection (including candidiasis).	Experienced in $\geq 1\%$ of patients.
Infrequent adverse effects.	Fever, vomiting, erythema, dermatitis, angioedema, seizures (especially in epileptics) and/or pseudo membranous colitis.	Experienced in 0.1 to 1 % of patients.
True anaphylaxis.	Hypersensitivity with hypotension, angioedema, bronchospasm and urticaria.	Experienced in 0.01 % of patients.

There are two clinical pictures that can result from penicillin allergy, namely acute and sub-acute reactions mediated by IgE and IgG antibodies respectively. The acute allergic reaction arises immediately or

rapidly within minutes to an hour or two and includes sudden anaphylaxis with hypotension, bronchospasm, angioedema and urticaria. Acute reactions result from reaction with preformed IgE to penicillin as a result of previous exposure. The resulting release of histamine and other mediators from mast cells produce the signs and symptoms typical of a true anaphylactic reaction. A less dramatic picture may occur 7 to 10 days after penicillin treatment starts or 1–2 days after repeat therapy. In this setting the picture is sub-acute and can include urticaria, fever and arthralgias or arthritis. The sub-acute reaction is caused by preformed IgG to penicillin as a result of previous penicillin treatment. The IgG antibody results in the activation of the complement reactions producing inflammation resulting in the symptoms mentioned earlier [2].

Many patients experience allergic reactions, but their symptoms do not coincide with an anaphylactic response as described above. So, it is currently considered relatively safe to administer the same antibiotic, and related ones if indicated, as long as it has been confirmed that the initial reaction was not IgE-mediated. This is, however, difficult to confirm in common pharmacy practice without the use of skin

sensitivity testing.

Penicillin skin sensitivity testing

Penicillin skin sensitivity testing can help to confirm the safety of the drug and quell fears of a dangerous drug reaction. A positive skin test indicates the presence of IgE antibodies to penicillin and immediately excludes the use of it and related β -lactam antibiotics. For non-penicillin β -lactams, the immunogenic determinants that are produced by degradation are unknown, and diagnostic skin testing is of limited value.

Persons with a history of penicillin “allergy” in whom skin testing yields a negative result have no greater risk of rashes associated with penicillin antibiotics than they do of rashes associated with any other class of antibiotics and are as much at risk of an allergic reaction as the general population. Thus, use of skin testing can increase the number of instances in which penicillin can be safely used rather than alternative broad-spectrum antibiotics, thereby helping to reduce the development of antibiotic resistance. Ideally, penicillin skin testing should be done in all persons with a history of penicillin allergy. Unfortunately, because of the lack of commercial penicillin skin test reagents, this is not possible. It should be noted that any skin sensitivity testing should be done by specially trained professionals

with access to a complete panel of penicillin skin test materials. There are times when doctors try to weaken and eventually overcome a patient’s sensitivity to the penicillin allergen through desensitization. They do this by administering small but gradually increasing doses of penicillin orally or intravenously. It is important, because desensitization can trigger a life-threatening reaction, hence it is only attempted in a controlled hospital setting and only when penicillin therapy is absolutely necessary [3].

Anaphylaxis

Risk management

Documentation or reporting of allergies often becomes inaccurate and many patients may report that they have an allergy to an antibiotic whereas they may have in fact experienced effects of the infection such as fever and diarrhoea. If a patient has exhibited signs of a true allergic reaction, re-exposure to penicillin or related antibiotics can trigger life-threatening anaphylaxis. It has been estimated that up to 60 % of penicillin-allergic patients will experience another allergic event if given the drug again. However, new data suggest that this rate is less than 2 %. Researchers analyzed data from more than 3 million patients on the UK General Practice Research Database, who had received at least one prescription for

penicillin. Of this group, 6212 (0.18 %) patients had experienced an allergic-like reaction after their initial penicillin prescription. Although these patients were 19 times less likely than others to receive a repeat prescription for penicillin, the percentage of allergic patients who received such prescriptions was high (48.5 %). With repeat penicillin use, those with an allergy were 11.2 times more likely than others to experience an allergic event. Despite this relative difference, the absolute risk of such events in the penicillin-allergic group was reported to be just 1.89%. The management of such an event therefore needs to focus on awareness to prevent re-exposure, knowledge of initial signs and symptoms such as wheezing, light-headedness, slurred speech, rapid or weaker pulse rate, blueness of skin, lips and nail beds, diarrhoea, nausea and vomiting along with emergency medical assistance and drug therapy to cope with the situation, particularly corticosteroids [3, 4].

In addition, we must be alert with respect to the use of various combination products which all contain penicillin. Serious medication errors can occur where doctors prescribe these medicines (often by brand name) and do not recognize that they contain penicillin.

Signs and symptoms of

anaphylaxis

Anaphylaxis, characterized by symptomatic hypotension with associated dyspnoea, urticaria, and possibly gastrointestinal (GI) symptoms, is the most severe manifestation of IgE-mediated drug allergy. It is most common after parenteral drug administration and is rare with oral or cutaneous exposure. Anaphylaxis results when antigen-specific IgE is present on mast cells and a systemic exposure to antigen occurs, cross-linking the IgE. This results in the simultaneous degranulation of large numbers of mast cells. Mast cells contain histamine and other vasoactive mediators. Their sudden release, due to either an IgE-mediated anaphylactic reaction or a similar non-IgE-mediated reaction (referred to as an “anaphylactic” reaction), results in a sudden drop in blood pressure and blood volume, flushing, itching, and potentially respiratory compromise, bowel oedema, and potential death (Table 2).

Drug therapy and emergency medical care

A mild allergic reaction can be treated with an antihistaminics like diphenhydramine, which helps relieve itching and skin rash. However, serious anaphylactic reactions require the urgent administration of

adrenalin to counter the cardiac collapse as well as corticosteroids to counteract the effect of the mediators released from the mast cell. In the case of a true anaphylactic hypersensitivity reaction, a patient may die unless controlled with adrenaline and their airway is maintained [5].

Table 2: Symptoms of anaphylaxis

IgE-mediated reactions	Clinical manifestations
•Hypotension	•generalized flushing of the skin
•Vasodilatation	•urticaria rash (hives) anywhere on the body
•Bronchospasm	•sense of impending doom
•Angioedema	•swelling of throat and mouth
•Bowel oedema	•alterations in heart rate
•Cardiovascular collapse	• severe asthma
	• abdominal pain, nausea and vomiting
	• sudden feeling of weakness (drop in blood pressure)
	• collapse and unconsciousness
Cross sensitivity	
There is partial cross-sensitivity	

between different types of penicillins. An individual who has exhibited immediate type of hypersensitivity with one penicillin should not be given any other type of penicillin. Until recently it has been accepted that there was up to a 10 % cross sensitivity between penicillin-derivatives, cephalosporins, and carbapenems, due to the sharing of the β -lactam ring. Recent papers have shown that the major determinant in the immunological reaction is the similarity between the side chain of first generation cephalosporins and penicillins, rather than the β -lactam structure that they share. This means that the risk of an allergic reaction to cephalosporins in those with an established IgE-mediated allergy to penicillin may be low or non-existent, as long as the side chains are not similar. The cephalosporin medications that are likely to cross-react after penicillin allergies have been established and include:

- Cephalexin
- Cefadroxil
- Cefaclor
- Cephadrine
- Cefprozil
- Ceftriaxone
- Cefpodoxime

Among those that lack the β -lactam side chain, and would therefore be safer, are:

- Cefazolin

- Cefuroxime
- Cefdinir
- Cefixime
- Ceftibuten

We should be aware that cephalosporin cross-reactivity in a penicillin-allergic patient is not necessarily a class effect. Dispensing of a prescription in a penicillin-allergic patient should be evaluated based on the type of allergic manifestations and the drug prescribed [6].

The other side of the discussion is whether those allergic to cephalosporins can safely receive penicillin. Anaphylactic reactions to cephalosporins are much less common than anaphylaxis associated with penicillin. Persons who make IgE in response to cephalosporins seem to produce it only in response to a particular cephalosporin, whereas persons who make clinically significant IgE in response to penicillin tend to react to core penicillin break-down products. Thus, in a patient with a history of a serious, potentially IgE-mediated reaction to a cephalosporin, it is critical to avoid re-exposure to the same cephalosporin, to a cephalosporin that shares the same side chain, and even to other β -lactams that share the same side chain (such as ceftazidime and aztreonam). Another thing to remember when thinking about medication for patients with a

penicillin allergy is that there is a three-fold increased coincidental risk of adverse reactions to even an unrelated drug. Penicillin-allergic patients are more likely to react to any class of drug, so extra care is required [7, 8].

Conclusion

Clinicians commonly encounter patients with a history of allergy to penicillin and other β -lactam antibiotics. However, it is known that about 90% of these patients are not truly allergic and could safely receive β -lactam antibiotics. The seriousness of the problem posed by drug allergies is perhaps overblown in part because of the loose use of the word "allergy," to refer to all immunologically mediated reactions. When assessing an allergy to penicillin the first issue is to establish whether or not a true allergic IgE mediated reaction has taken place. Instead, these patients are often treated unnecessarily with an alternate broad spectrum antibiotic, which could increase costs and contribute to the development and spread of multiple drug-resistant bacteria.

The frequently cited figures of 10 % cross reactivity between penicillin and cephalosporin is perhaps an overestimate. The degree of cross-reactivity between cephalosporins and penicillins depends on the generation of cephalosporins, being

higher with earlier generation cephalosporins. Cross reactivity between penicillin and second and third generation cephalosporin is low and may be lower than the cross reactivity between penicillin and unrelated antibiotics. In addition, the frequency of immediate allergic reactions to cephalosporins is considerably lower compared to penicillins, and cross-reactivity among cephalosporins is lower compared to cross-reactivity between penicillin and cephalosporins.

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